REMARKS

Claim 6 has been amended to more clearly recite the subject matter Applicants regard as the invention, and is believed to more clearly specify the disorders to be diagnosed in the practice of the claimed invention. Support for the amendments to claim 6 may be found, for example, in the application at page 3, lines 3-5; page 10, lines 20-25; page 91, lines 9-13; and elsewhere in the application as originally filed. Subject matter deleted from claim 6 is deleted without acquiescence to any rejections and without prejudice to prosecution of such subject matter in related divisional, continuation, and continuation-in-part applications.

No new matter is added by way of the amendments to the claims.

Pending claim 6 is a linking claim linking the claimed methods directed to the several disorders recited in dependent claims 7-11; dependent claims 7 and 8, directed to malignancies, are believed to recite subject matter elected pursuant to the Restriction Requirement, which has been made final. Applicants have listed claim 9 as "withdrawn" as encompassing disorders including but not limited to malignancies. Dependent claims 9-11 stand withdrawn as directed to non-elected subject matter, which, upon allowance of linking claim 6, the restriction requirement as to the linked inventions shall be withdrawn and any claims, such as claims 9-11, depending from or otherwise including all limitations of the allowable linking claims will be entitled to examination in the present application.

Applicants acknowledge the withdrawal of the rejections of claims 6-9 under 35 U.S.C. § 112, Second Paragraph.

Claims 6-9 stand rejected under 35 U.S.C. § 112, First Paragraph, as allegedly lacking enablement. Applicants respectfully traverse the rejection.

The Rejections of Claims 6-9 and 12 under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 6-9 stand rejected under 35 U.S.C. § 112, First Paragraph, as allegedly lacking enablement for a method of diagnosis of malignancy (page 3 of the instant Office Action).

The Wands Factors

As discussed in previous amendments, Applicants' analysis of the claims in view of the factors enumerated in *In re Wands* (8 USPQ2d 1400 (Fed. Cir. 1988)) results in the conclusion that the present claims are enabled by the disclosure of the specification as filed and in view of the skill and knowledge of one of ordinary skill in the art.

Applying the *In re Wands* factors to the present claims, we find that:

1) The nature of the invention:

The claims are drawn to methods for diagnosis of pathological conditions, and, in view of the Restriction Requirement, are examined with respect to the pathological condition of malignancy. The claimed methods require one of ordinary skill in the art to contact a biological sample with a detectably labeled polypeptide (comprising either SEQ ID NO:2 or SEQ ID NO:4) and to detect either a) overexpression of neurotrophic factor NT-4/5, or b) underexpression of neurotrophic factor NT-4/5 (where the overexpression or underexpression is as compared such expression in a sample from a normal subject). Applicants submit that such methods are clear, straightforward, and well within the ability of one of ordinary skill in the art to reliably carry out. Thus the nature of the invention is not complex and its practice by one of ordinary skill in the art would quickly and readily become routine.

The USPTO suggests that the claimed method is not routine, apparently considering the trkB receptors SEQ ID NO:2 and SEQ ID NO:4 as not being specific probes for SEQ ID NO: 45, and apparently concerned that the target neurotrophic factor NT-4/5 as not being specific for a trkB receptor. However, Applicants note that the claimed methods recite specific molecules as probes and as targets, that the amino acid sequences of these probes and targets are disclosed in the application, and that their use is disclosed in the application. Accordingly, since the probes and targets are specifically disclosed, since the application provides sufficient teaching so that one of ordinary skill in the art would know how to practice the claimed methods, Applicants submit that the nature of the invention is routine in the art.

2) The state of the prior art:

As discussed in previous amendments, the prior art provides to one of ordinary skill in

the art the requisite skills and knowledge needed to practice the claimed invention, including, in view of the teaching of the application, methods for detecting the overexpression and underexpression of the neurotrophic factor SEQ ID NO:45. Measurement of levels of a molecule of interest in normal tissue as well as in diseased tissue was well known, as was the comparison of levels of a molecule of interest in control and in test tissue samples.

The USPTO has expressed concern that the trkB receptor SEQ ID NO:2 or SEQ ID NO:4 may not be specific for SEQ ID NO:45 since the trkA receptor also binds SEQ ID NO:45. However, even though trkB and trkA bind SEQ ID NO:45 (see, e.g., page 4, lines 8-12 of the present application), Applicants note that the state of the prior art, in view of the disclosure of the application, makes the claimed methods understandable and within the capability of one of ordinary skill in the art.

Applicants further note that whether or not other neurotrophins may bind to trkB receptors, it is clear that NT-4/5 (SEQ ID NO:45) binds to trkB receptors SEQ ID NO:2 and SEQ ID NO:4. Such binding provides a basis for the working of the claimed methods, and enables one of ordinary skill in the art to readily perform these methods. These methods are practical and workable, as claimed, since alterations in levels of NT-4/5 binding to detectably labeled trkB receptors in a sample, as compared to levels of NT-4/5 binding to detectably labeled trkB receptors in normal samples is enabled by the application regardless of whether or not other neurotrophins may bind to trkB receptors.

Although the USPTO suggests that Applicants' discussion of Schneider et al. is not persuasive, stating that Schneider et al. used an anti-NT-4 antibody "which is specific for NT-4" (page 4 of the instant Office Action), Applicants submit that it is not significant that Schneider et al. used an antibody, while the present claims are directed to the use of a detectably labeled human trkB receptor polypeptide comprising SEQ ID NO:2 or SEQ ID NO:4, or an immunoadhesin thereof capable of binding said neurotrophic factor, since both an antibody and a detectably labeled human trkB receptor polypeptide comprising SEQ ID NO:2 or SEQ ID NO:4, or an immunoadhesin thereof capable of binding said neurotrophic factor are effective to bind SEQ ID NO:45 as required by the claims. Thus, the claimed invention is operable and enabled

by the specification, regardless of whether or not an alternative method, using an antibody, would or would not be more specific.

Applicants note that, although an invention must work for its intended purpose, an invention need not be perfect. As the U.S. Supreme Court stated in *Hildreth v. Mastoras*, 257 U.S. 27, 34 (1924) "The machine patented may be imperfect in its operation; but if it embodies the general principle and works ... it is enough." Similarly, as stated in *Decca, Ltd. V. United States*, 544 F.2d 1070, 191 USPQ 439 (Ct. Cl. 1976) "The mere fact that the system has some drawbacks, or that under certain postulated conditions it may not work... does not detract from the operability of the disclosed equipment to perform its described function." These cases were cited with approval by the Federal Circuit, which stated that it "is indeed correct that a claim is not invalid for lack of operability simply because the invention does not work perfectly under all conditions" (National Recovery Technologies v. Magnetic Separation Systems, Inc. 166 F.3d 1190, 1196, 49 USPQ2d 1671, 1676 (Fed. Cir. 1999)).

Thus, in view of the state of the art, Applicants submit that the claimed invention is enabled by the specification.

3) The relative skill of those in the art:

Applicants acknowledge the USPTO's agreement that the relative skill of those in the art is high (page 5 of the instant Office Action). However, the USPTO suggests that undue experimentation would be required to practice the claimed method, because one of ordinary skill in the art would allegedly not be able to "predict the level of SEQ ID NO:45 in the claimed genus of numerous cancers, as compared to that of normal, healthy individual" (page 5 of the instant Office Action, citing Soontornniyooomkij et al. and Guate et al.).

In response, Applicants note that the claimed methods do not require knowledge of the level of SEQ ID NO:45 that is indicative of cancer, but instead diagnose the selected pathological condition by determining if the level of expression of SEQ ID NO:45 is either a) greater, or b) lesser than the level of expression of SEQ ID NO:45 in a sample from a normal subject.

The USPTO again is also concerned that "[t]he claimed method is non-specific because the probe for use in the claimed method is non-specific" and that the presence of BDNF and NT-3 "would interfere with detection of SEQ ID NO:45 (page 6 of the instant Office Action). However, as discussed above, although trkB receptors SEQ ID NO:2 and SEQ ID NO:4 may not bind SEQ ID NO:45 as specifically as would, for example, an antibody to an epitope of SEQ ID NO:45, this does not negate the fact, disclosed in the present application, that trkB receptors SEQ ID NO:2 and SEQ ID NO:4 do indeed bind SEQ ID NO:45 and may be used in the practice of the claimed methods as disclosed and enabled by the specification. Applicants further note that there is no reason to believe that BDNF and NT-3 would be expressed at all, or would be expressed at differential levels in all samples, and so there is no reason to assume that such postulated "interference" would occur or would be a significant factor in the practice of the invention. Applicants note that even if such interference might be possible, "a claim is not invalid for lack of operability simply because the invention does not work perfectly under all conditions" (National Recovery Technologies v. Magnetic Separation Systems, Inc. 166 F.3d 1190, 1196, 49 USPQ2d 1671, 1676 (Fed. Cir. 1999)).

Thus, Applicants respectfully submit that the alleged concerns raised by the USPTO do not support a conclusion that undue experimentation would be required to practice the invention, nor that the specification does not enable one of ordinary skill in the art to practice the invention.

4) The predictability or unpredictability of the art:

Applicants note that the USPTO acknowledges that a "method of measuring the level of a protein is routine in the art" (page 7 of the instant Office Action). However, the USPTO again suggests, citing Soontornniyooomkij et al. and Guate et al., that (other than pancreatic cancer) "one cannot predict the level of SEQ ID NO:45 in the claimed **genus of numerous cancers**, as compared to that of normal healthy individual" (emphasis in the original), and that the "claimed method is **non-specific**, because the probe for use in the claimed method is non-specific" (page 7 of the instant Office Action).

Applicants have addressed these concerns previously, including as discussed above. Applicants again note that the present claims are directed to diagnoses based on differences

between levels measured in a test tissue sample and a normal tissue sample, so that prior knowledge of absolute levels is not required to practice the claimed methods, and that whether or not one characterizes probe binding as "non-specific" or not, it is clear that the probe recited in the claims does indeed bind to the target molecules, so that the claimed methods are indeed enabled, and one of ordinary skill in the art could indeed successfully use the SEQ ID NO:2 or SEQ ID NO:4 to bind SEQ ID NO:45 as recited in the claims.

The USPTO is also concerned that one of ordinary skill in the art might not predict that SEQ ID NO:4 retains the binding region for the ligand SEQ ID NO:45, and so might not bind its ligand. However, inspection of Fig. 16, for example, indicates that the 476 amino acid truncated version of trkB (SEQ ID NO:4) would include the Cysteine Rich I, Leucine Rich, Cysteine Rich II, Immunoglobulin I, Immunoglobulin II, Transmembrane, and much of the Juxtamembrane regions, while lacking the tyrosine kinase region. Applicants submit that one of ordinary skill in the art would expect that the regions remaining in the truncated trkB would be ligand binding regions, and that the loss (through truncation) of the tyrosine kinase region (typically an intracellular region not directly involved with ligand binding, but instead being typically an effector region modulated by ligand binding) would not be expected to have a significant impact on the ability of SEQ ID NO:4 to bind SEQ ID NO:45. Thus, Applicants submit that the disclosure of the application, as originally filed, in view of the knowledge and skill of one of ordinary skill in the art, would allow one of ordinary skill in the art to predict that one could successfully use SEQ ID NO:4 for detecting the presence of SEQ ID NO:45.

5) The breadth of the claims:

The USPTO suggests that the claims are broad encompassing a method for diagnosis of a number of cancers, which over or underexpress SEQ ID NO:45, using a probe which is non-specific for the target SEQ ID NO:45 (page 8 of the instant Office Action). However, Applicants respectfully submit that the claims are narrowly drawn to methods directed to specific steps that require the use of identified molecules. The claimed methods require the use of detectably labeled SEQ ID NO:2 or detectably labeled SEQ ID NO:4, or an immunoadhesin thereof; and require detecting binding of these molecules to SEQ ID NO:45. Being limited to these particular

methods and particular molecules, Applicants submit that these narrow, focused methods are not broad.

6) The amount of direction and the absence of working example

The USPTO acknowledges that the specification and the art disclose how to measure the level of the neurotrophin factor, but suggests that the specification and art do not disclose, nor have any concrete evidence regarding which cancer under-or over-expresses the claimed neurotrophic factor, SEQ ID NO:45, as compared to the normal corresponding control, and suggests that the specification lacks data or concrete evidence that SEQ ID NO:2, SEQ ID NO:4, or an immunoadhesin thereof, is a suitable, specific probe, and only detects SEQ ID NO:45 (page 9 of the instant Office Action). However, as discussed above, the specification and the art provide evidence that one of ordinary skill in the art could use to enable the practice of the invention by using detectably labeled SEQ ID NO:2, SEQ ID NO:4, or an immunoadhesin thereof, to detect SEQ ID NO:45 in test samples and in samples from normal tissue, thereby to diagnose a malignancy characterized by overexpression or underexpression of SEQ ID NO:45.

In addition, as discussed above, the specification and the art provide evidence that SEQ ID NO:2, SEQ ID NO:4, or an immunoadhesin thereof, bind SEQ ID NO:45, and thus that these molecules are suitable and effective probes, and suitable for the practice of the claimed invention. It appears that the USPTO is concerned that other probes, such as possibly an antibody, might provide more specific probes. However, as discussed above, a claimed invention need not be perfect, nor need it be better in all respects than other possible methods; Applicants submit that the present invention, as disclosed in the application and as claimed in the present claims, is supported and enabled by the specification.

Summary

The USPTO concludes on page 9 of the instant Office Action by suggesting that there is a lack of sufficient disclosure in the specification, and in the art, and that one of ordinary skill in the art would require undue experimentation to practice the claimed invention. However, Applicants note that the application discloses and teaches methods for measuring neurotrophin levels in tissue, which can be normal or diseased tissue. The application and the art teach that

NT-4/5 (SEQ ID NO:45) binds to trkB receptors SEQ ID NO:2 and SEQ ID NO:4. Such binding provides a basis for the working of the claimed methods, and enables one of ordinary skill in the art to readily perform these methods. As discussed above, and as acknowledged by the USPTO, the relative skill of those in the art is high, and a method of measuring the level of a protein is routine in the art. The claimed methods require the detection of differences between protein levels measured in a test tissue sample and a normal tissue sample, and do not require any prior knowledge of the absolute levels of the target proteins in order to practice the claimed methods. Although the USPTO appears to have some concern that other, possibly more specific, probes might exist, the present claims are not directed to the use of such other, possible probes, but instead disclose and require the use of probes known in the art to bind to the target molecules. Thus, the claimed methods are indeed enabled, and one of ordinary skill in the art could indeed successfully use the SEQ ID NO:2 or SEQ ID NO:4 to bind SEQ ID NO:45 as recited in the claims.

Applicants submit that the application provides sufficient guidance and direction as to enable one of ordinary skill in the art to practice the invention without undue experimentation. Accordingly, in view of the teaching of the application, and in view of the analysis of the *In re Wands* factors indicating that the amount of experimentation required to practice the invention is not undue, Applicants submit that the claims are enabled and that the rejections of claims 6-9 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement are overcome.

CONCLUSION

The amendments place the claims in condition for allowance or in better form for consideration on appeal, and do not require a new search by the Examiner. Entry of the amendments is respectfully requested.

Applicants respectfully request consideration and allowance of claims 6-8 as amended. In view of the allowable subject matter of the linking claim, claim 6, Applicants further request that the restriction requirement be withdrawn and that the remaining, withdrawn claims 9-11 and their subject matter be examined and allowed. Early notification of the allowance of the application is respectfully requested.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Although no fees are believed to be due, please charge any fees due, including any fees for extension of time and for any other fees due, to Deposit Account No. **07-1700** **(referencing Attorney's Docket No. GNE-0033 P2C3)**.

Respectfully Submitted,

Date: April 11, 2008

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